The BOADICEA model of genetic susceptibility to breast and ovarian cancer: updating, validation and predictions.

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Several genes conferring susceptibility to breast and ovarian cancer, notably BRCA1 and BRCA2, have been identified. The majority of the familial aggregation to breast cancer is, however, not explained by these genes. We have previously derived a susceptibility model using segregation analysis of breast and ovarian cancer occurrence in a combined dataset, including a population-based series of 1,484 breast cancer cases and 156 high-risk families from the UK (Antoniou et al., *Br J Cancer*, 2002). We are currently updating this model using additional data from two UK population-based studies of breast cancer (Peto et al., *JNCI*, 1999; Lalloo et al., *Lancet*, 2003) and data from the meta-analysis of the families of BRCA1/2 carriers identified through population-based studies of breast and ovarian cancer (Antoniou et al., *AJHG*, 2003). At least one individual from each family had been tested for BRCA1 and BRCA2 mutations. In total, our dataset includes 2,785 families, among which 301 segregate mutations in BRCA1, and 236 segregate mutations in BRCA2.

According to this model, susceptibility to breast cancer is explained by mutations in BRCA1 and BRCA2, together with a polygenic component, reflecting the joint multiplicative effects of multiple genes of small effect on breast cancer risk. The model also incorporates the effect of genetic modifiers on breast cancer risk in BRCA1 and BRCA2 mutation carriers. A birth cohort effect on the breast and ovarian cancer risks is implemented whereby each individual is assumed to develop cancer according to calendar period-specific incidence rates. Finally, the model allows for the reduced sensitivity of the mutation detection method used. The population frequency of BRCA1 mutations is estimated to be 0.06% (95%CI 0.04-0.10%), and that of BRCA2 mutations is 0.10% (0.07-0.15%). The variance of the polygenic component is age dependent and declines with age from 3.6 at age 20 to 0.7 at age 70. The model predicts that the average breast cancer risks in BRCA1 and BRCA2 carriers are cohort specific, with the risks increasing in more recent birth cohorts. For example, the average cumulative breast cancer risk to BRCA1 carriers is 50% for women born in 1920–1929 and 58% for women born after 1950.

The overall familial risks of breast cancer predicted by this model are close to those observed in epidemiological studies. The predicted prevalences of BRCA1 and BRCA2 mutations among unselected cases of breast and ovarian cancer are also consistent with observations from population-based studies. These predictions are closer to the observed values than those obtained using the Claus model (Claus et al., *AJHG*, 1991) or BRCAPRO (*CancerGene* v.3.1). Since breast cancer risks in BRCA1 and BRCA2 carriers are modified by the polygenic component, the predicted risks to carriers are dependent on family history; this appears to be consistent with the variation in penetrance estimates found in different studies. We conclude that this model provides a rational basis for risk assessment in individuals with a family history of breast or ovarian cancer. Future work and extensions will also be discussed.